(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 2 351 758 A1**

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 153(4) EPC

(43) Date of publication:
**03.08.2011 Bulletin 2011/31**

(21) Application number: **08877097.9**

(22) Date of filing: **05.12.2008**

(51) Int Cl.:
***C07F 5/00*** *(2006.01)* ***C07F 13/00*** *(2006.01)*
***A61K 51/00*** *(2006.01)* ***A61P 35/04*** *(2006.01)*

(86) International application number:
**PCT/RU2008/000748**

(87) International publication number:
**WO 2010/036140 (01.04.2010 Gazette 2010/13)**

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MT NL NO PL PT RO SE SI SK TR**

(30) Priority: **29.09.2008 RU 2008138587**

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# (54) METAL COMPLEXES, A METHOD FOR PREPARING SAME, RADIOPHARMACEUTICAL MEANS BASED THEREON

(57) The invention relates to the new metal complexes of the formula $M(O)_K H_m A^{n-}$, wherein M is the isotope of Tc, Re, Sm, Lu, Y, H is the hydrogen, $A^{5-}$ is the anion of the zoledronic acid, wherein, when M is the technetium, then K=1, m=1, n=2; when M is the rhenium, then K=1, m=1, n=2; when M is the samarium, lutetium, or yttrium, then K=0, m=2, n=3, and their pharmaceutically eligible salts, hydrates, or isomers. The invention also relates to the method of production of the metal complex, wherein the lyophilizate obtained by mixing the zoledronic acid and tin dichloride solutions in the hydrochloric acid under inert gas and adding a hydroxide of an alkaline metal is mixed with a salt of a metal from the isotopes group and a radionuclide solution. What is proposed is the radiopharmaceutical that contains the metal complexes, their pharmaceutically eligible salts, hydrates, or isomers, and antioxidant, and the method of production of the radiopharmaceutical, wherein the lyophilizate is mixed with the solution containing a salt of a metal from the isotopes group and the radionuclide solution.

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## Description

**[0001]** The invention relates to the chemistry and medicine, in particular, to the metal complexes, a method of their production, radiopharmaceutical compositions on their basis and a method of their production, and can be used for the diagnostics and treatment in the oncology, namely, in the therapy of the myelogenic disease, osseous metastases at the mammary gland, lungs, thyroid, colon, uterine body, prostate carcinomas, and as a mean to reduce the hypercalcemia.

**[0002]** The complexes of radionuclides with the di- and poly-phosphonates have the ability to selectively accumulate in the skeleton, especially in the pathologic osteogenesis zones. The main advantage of the skeleton scintigraphy compared with the traditional X-ray diagnostics is the early detection of both the single and multiple loci of increased accumulation at the malignant neoplasms of the osseous skeleton and bone metastases.

**[0003]** Currently known are the $^{99m}$Tc phosphate complexes, in particular the polyphosphate, triphosphate, and pyrophosphate [G.Subramanian, J.G.Agfee//Radiology-1971.-Vol.99.-p.192].

**[0004]** Currently known are also the diphosphonates $^{99m}$Tc, with similar properties [Schmitt G.H., Holmes R.A., Isitman AT. //Radiology-1974.-Vol.112.- p.733].

**[0005]** As of today, the world radiological practice uses essentially the $^{99m}$Tc-methylenediphosphonate ($^{99m}$Tc-MDP) and $^{99m}$Tc-hydroxyethylidene-diphosphonate ($^{99m}$Tc-HEDP) [W.C.Eckelman, W.A.Volkert. //Int.J.Appl.Radiat.Isotopes-1982.-Vol.33.-p.945]. To receive the $^{99m}$Tc the pertechnetate, sodium $^{99m}$Tc, obtained from the $^{99}$Mo/$^{99m}$Tc generator is used. The Tc(VII) is the most chemically stable state of the technetium; however, the pertechnetate ions do not combine with the chelating agents. To receive the stable compounds of the reduced technetium different reducers are needed, such as the tin ions (II), sodium boron hydride, concentrated hydrochloric acid, sodium dithionite, and hydrazine [Nuclear Medicine. Diagnosis and Therapy//J.C.Harbert, W.C.Eckelman, R.D.Neumann Eds.-Thieme Medical Publishers, Inc., New York, 1990, p. 218]. As of the reducer, the tin dichloride that is a constituent of practically all the $^{99m}$Tc preparations is the most widely used. As the tin dichloride is in a great excess in relation to the $^{99m}$Tc, it supports the technetium in the reduced form and supports the formation of the reduced technetium complex with the ligands.

**[0006]** All the technetium complexes with the diphosphonates are osteotropic; hence, the "$^{99m}$Tc-phosphonate complex" is a standard formulation.

**[0007]** Alongside with the $^{99m}$Tc, the radionuclide therapy uses the rhenium and samarium isotopes, in particular, the $^{153}$Sm-ethylenediaminetetramethylenephosphate ($^{153}$Sm-EDTMP) [Resche I.,Catal J.F.,Peching A. //Eur. J/ Cancer. - 1997. -Vol.33, p.1583], samarium-153-oxabifor [Krylov V.V., Tsyb A.F.,Drosdovsky B.Y. //Eur.J.Nucl.Med. and Molec.Imaging.-2006.- Vol.33, Suppl. 2.- s. 335], rhenium-186- and rhenium-188-hydroxyethylenediphosphonate ($^{186}$Re-HEDP [Jak M.S.P., Han S.H. Zonnenberg B.A, et al.//J.Nucl.Med.- 1996.-Vol.37.- p.1511], $^{18}$Re-HEDP [Faintuch B.L.Faintuch S., Muramoto E. // Radiochim.Asta- 2003.- Vol. 91.- p.607] , $^{188}$-Re-methylenediphosphonate ($^{188}$Re-MDP) [Hashimoto K., Bagiawati S.Jzumo M., Kobayashi K. //Appl. Radiat. Isot.-1996-Vol. 47, No.2-p.195].

**[0008]** The rhenium-186 is obtained in a nuclear reactor, in the reaction $^{185}$Re (n,$\gamma$) $^{186}$Re, or in a cyclotron, in the reaction $^{186}$W (p, n) $^{186}$Re [Jak M.S.P., Han S.H., Zonnenberg B.A. et al. //J. Nucl. Med.- 1996.-Vol.37.-p. 1511]. These methods are expensive enough. The rhenium-188 generator was developed wherein the parent isotope was the W-188, received from the W-186 concentrated metallic tungsten or tungsten oxide [Knapp F.F. Mirzadeh S., Zamora P.,et al .// Nucl. Med. Commun.-1996.-Vol. 17.-p. 268].

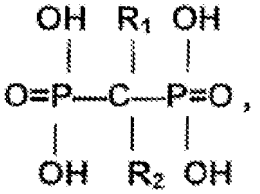
**[0009]** The rhenium, just like the technetium, forms complexes with different ligands. The processes of the rhenium-188 formation with the three methylenephosphonic acids, namely, the ethylenediamine-N,N,N',N'-tetrakis(methylenephosphoric acid, EDTMP; (ethylenediamine-N,N'-bis-methylenephosphoric acid, EDBMP); (nitrilotris-methylenephosphoric acid, NTMP) were studied. It was noted that in presence of the tin dichloride all the ligands form complexes at the pH < 3 [Hashimoto K. The Second Japanese-Russian Seminar on technetium. Shizuoka, Japan, 1999, Abstracts.-p. 40.].

**[0010]** Along with the diphosphonates, the medical practice often uses the biphosphonates [Bonevolenskaya L.I. Biphosphonates and Osteoporosis.// Handbook on Osteoporosis/ Ed.by Bonevolenskaya- Moscow, Binosh, Laboratoriya znaniy.-2003.-CH.9.-p.196-216.]. The biphosphonates acute, subacute, and chronic toxicity studies show that they are, in whole, in the group of the low toxicity compounds with the relatively low acute and chronic toxicity levels. Neither have they demonstrated the teratogenic, mutagenic, or carcinogenic properties.

**[0011]** The zoledronic acid is a biphosphonate and can inhibit the osseous resorption. The anti-resorptive mechanism is not completely clear. In vitro, the zoledronic acid inhibits the activity and induces the apoptosis of the osteoclasts. It blocks the osteoclastic resorption of the mineralized osseous and cartilaginous tissues.

**[0012]** In Storto G., Paone G., Ibello F., et al. // Eur.J. Nucl. Med. And Molec.Imaging.-2004.- Vol. 31, - s. 291. the authors applied the combined Sr-89 + zoledronic acid therapy to reduce the osseous pains at the metastases resulting from the mammary gland and prostate gland carcinomas; they compared the results with those of the therapy using only the Sr-89.

**[0013]** As of today, the skeleton scintigraphy (diagnostics) uses, mainly, the simplest technetium-$^{99m}$-labeled diphosphonates of the general formula:



where $R_1$ and $R_2$ denote the hydrogen, hydroxy, carboxy, hydrocarbonic radical, e.g., the methylenediphosphonate (MDP), oxyethyldiphosphonate (HEDP) or dicarboxydiphosphonate (OPP) [W.C.Eckelman, W.A.Volkert. //I nt.J.Appl. Rad iat. Isotopes- 1982.-Vol.33.-p.945] and the rhemium-186 or rhenium-188-labeled diphosphonates, mainly the oxyethylidenediphosphonate [Jak M.S.P., Han S.H. Zonnenberg B.A, et al.// J.Nucl.Med.- 1996.-Vol.37.- p.1511], $^{188}$Re-HEDP [Faintuch B.L.Faintuch S., Muramoto E. // Radiochim.Asta- 2003.- Vol. 91.- p.607].

**[0014]** However, their specificity, diagnostic sensitivity, and treatment efficiency are not sufficiently high.

**[0015]** The purpose of this invention is to overcome the above-listed shortcomings.

**[0016]** The objective is reached by the inventions relative to the proposed metal complexes and based on them radiopharmaceuticals and to the method of production of the radiopharmaceutical.

**[0017]** The formula of the proposed metal complexes is the following:

$$M(O)_K H_m A^{n-},$$

where M is the isotope of Tc, Re, Sm, Lu, Y, H is hydrogen, $A^{5-}$ is the anion of the zoledronic acid,
wherein, when M is the technetium, then K=1, m=1, n=2; when M is the rhenium, then K=1, m=1, n=1; when M is the samarium, lutetium, or yttrium, then
K=0, m=1, n=1.

**[0018]** The proposed metal complexes are the complexes of the isotopes of the metal of the group with the zoledronic acid and their pharmaceutically eligible salts, hydrates, or isomers.

**[0019]** The metals isotopes are selected from the group consisting of the $^{186,188}$Re, $^{99m}$Tc, $^{153}$Sm, $^{177}$Lu, $^{90}$Y, wherein the preferable metals isotopes are the $^{186,188}$Re, $^{99m}$Tc.

**[0020]** The reducing agents are the tin halogenide, sodium boron hydride, or sodium dithionite; the selected tin halogenide is either tin dichloride or tin fluoride.

**[0021]** The proposed method of production of the metal complex comprises that the lyophilizate obtained by mixing the zoledronic acid and tin dichloride solutions in the hydrochloric acid under inert gas and adding a hydroxide of an alkaline metal is mixed with a salt of a metal from the isotopes group and a radionuclide solution.

**[0022]** The proposed radiopharmaceutical contains the metal complexes, their pharmaceutically eligible salts, hydrates or isomers in accordance with claim 1, and an antioxidant, either the ascorbic acid or the gentisinic acid.

**[0023]** The method of production of the radiopharmaceutical comprises mixing the lyophilizate with the solution containing the metal salt and the radionuclide solution.

**[0024]** The proposed metal complexes may contain ascorbic or gentisinic acid serving as antioxidants.

**[0025]** The examples below illustrate the production of the proposed complexes and radiopharmaceutical.

**Example 1:**

**Synthesis of the preparation with the technetium-$^{99m}$:**

**1. Preparation of the lyophilized reagent**

**[0026]** 0.15 grams of the zoledronic acid were dissolved in 92 ml of water in an inert gas flow. This and following operations were performed in an inert gas flow. To the resulting solution, 5 ml of the tin dichloride solution in 1 M hydrochloric acid (6-7 mg/ml) and 3 ml of the 1.5 M NaOH solution were added. The resulting reagent solution was passed through the 0.22 μm filter and packed in the medicinal vials by 1 ml portions. The vials contents were lyophilized.

**2. Composition of lyophilizate in vial:**

**[0027]**

| | |
|---|---|
| zoledronic acid | 1.53 mg |
| tin dichloride, anhydrous | 0.3 mg |
| pH | 4-6,5 |

**3. Preparation**

**[0028]** In the lyophilized reagent vial, 5 ml of the isotonic solution of the sodium pertechnetate, $^{99m}$Tc (740-1480 MBq/ml) from the generator were added; this was cured 20 minutes under the room temperature.

**4. Composition of preparation:**

**[0029]**

| | |
|---|---|
| Technetium-$^{99m}$ in form of complex with zoledronic acid | 740-1480 MBq/ml |
| zoledronic acid | 0.31 mg/ml |
| tin dichloride, anhydrous | 0.06 mg/ml |
| pH | 4-6 |
| Radiochemical purity (determined by the HELC and TLC methods) | > 95 % |

**Example 2:**

**Synthesis of preparation with the rhenium-188**

**1. Preparation of the lyophilized reagent**

**[0030]** 0.42 grams of the gentisinic acid were dissolved in 60 ml of water. This and following operations were performed in an inert gas flow. To the resulting solution, 8 ml of the tin dichloride solution in 1 M hydrochloric acid (18 mg/ml) and 40 ml of the zoledronic acid aqueous solution (6 mg/ml) were added. The resulting reagent solution was passed through the 0.22 μm filter and packed in the medicinal vials by 1 ml portions. The vials contents were lyophilized.

**2. Composition of lyophilized reagent in vial:**

**[0031]**

| | |
|---|---|
| zoledronic acid | 2.2 mg |
| tin dichloride | 1.33 mg |
| gentisinic acid | 3.9 mg |
| pH | 2,4 |

**3. Preparation:**

**[0032]**

a) Into the vial with 40 μl of the sodium perrhenate of the 0.8 mg/ml rhenium concentration, 1.5 ml of the sodium perrhenate, $^{188}$Re, solution was added. The solution was stirred (vial No 2).
b) Into the vial with the lyophilized reagent (vial No 1), all the content of the vial No 2 was transferred with the help of a syringe; then it was stirred.
c) The preparation was kept under room temperature within 2 hours. Before use, the preparation solution was passed through the 0.22 μm filter.

**4. Composition of preparation:**

**[0033]**

| | |
|---|---|
| rhenium-188 in form of complex with zoledronic acid | 740-7400 MBq/ml |
| zoledronic acid | 1.45 mg/ml |
| tin dichloride | 0.89 mg/ml |
| gentisinic acid | 2.59 mg/ml |
| rhenium | 0.02 mg/ml |
| pH | 2-4 |
| Radiochemical purity (determined by the HELC and TLC methods) | > 90 % |

**[0034]** The other metal complexes are produced similarly to Examples 1 and 2.

**Biological testing of proposed metal complexes**

**[0035]** The experiments were run on the intact scrub albino rats with modeled osseous pathology. The osseous pathology was imitated by the femur fracture.

**[0036]** To prepare the composition, 5.0 ml of the sodium pertechnetate $^{99m}$Tc from the technetium generator (FSP 42-0225-4528-03, FSP 42-0018-2694-02) were injected into the lyophilizate vial by puncturing the rubber stopper with a syringe needle; then the vial was agitated and cured 20 minutes. The 0.2 ml volume of the composition was injected into the caudal vein. 1, 3, 5, and 24 hours after injection the animals were devitalized by decapitation; then the samples of blood, liver, kidneys, stomach, right and left femurs, urinary bladder with contents were taken. The radionuclide in organs and tissues was determined by the direct radiometry.

**[0037]** The delayed retention index was determined as the ratio of division of the composition concentration in the femoral bone with the modeled osseous pathology and in the healthy femoral bone.

**[0038]** The statistical treatment used the Student's method.

**[0039]** The results are given in Tables 1 and 2.

**Table 1** Pharmacokinetics of "zoledronic acid, $^{99m}$Tc" in organs and tissues of intact female rats after intravenous introduction (% dose/organ).

| Organ/tissue | 1 h | 3 h | 5 h | 24 h |
|---|---|---|---|---|
| Blood | 1.7 ± 0.27 | 0.9 ± 0.38 | 0.4 ± 0.03 | traces |
| Liver | 0.8 ± 0.12 | 1.0 ± 0.27 | 0.6 ± 0.11 | 0.2 ± 0.13 |
| Kidneys | 1.3 ± 0.17 | 0.9 ± 0.21 | 1.2 ± 0.13 | 0.6 ± 0.32 |
| Stomach | 0.1 ± 0.03 | 0.1 ± 0.01 | 0.1 ± 0.04 | 0.3 ± 0.05 |
| Urinary bladder (1, 3 h); | 45.4 ± 4.03 | 30.1 ± 4.41 | | |
| Excretion (5, 24 μ) | | | 52.4 ± 2.80 | 39.1 ± 5.00 |
| Femur | 1.8 ± 0.16 | 1.9 ± 0.35 | 1.6 ± 0.11 | 1.8 ± 0.06 |
| Skeleton | 48.1 ± 4.36 | 47.3 ± 2.89 | 42.9 ± 2.93 | 49.6 ± 1.77 |

**Table 2** Pharmacokinetics of "zoledronic acid, $^{99m}$Tc" in organs and tissues of female rats with modeled osseous pathology after intravenous introduction (% dose/organ).

| Organ/tissue | 1 h | 3 h | 5 h | 24 h |
|---|---|---|---|---|
| Blood | 1.7 ± 0.71 | 2.0 ± 0.81 | 0.5 ± 0.01 | 0.7 ± 0.01 |
| Liver | 1.7+0.58 | 1.1 ± 0.42 | 1.0 ± 0.05 | 0.5 ± 0.09 |
| Kidneys | 1.8 ± 0.83 | 1.4 ± 0.68 | 0.9 ± 0.06 | 0.5 ± 0.08 |
| Stomach | 0.4 ± 0.03 | 0.2 ± 0.09 | 0.4 ± 0.05 | traces |

(continued)

| Organ/tissue | 1 h | 3 h | 5 h | 24 h |
|---|---|---|---|---|
| Urinary bladder (1, 3 h); | 35.1 ± 10.53 | 44.8 ± 3.89 | | |
| Excretion (5, 24 μ) | | | 43.4 ± 5.05 | 52.5 ± 10.86 |
| Femur, normal | 2.1 ± 0.20 | 1.9 ± 0.42 | 1.9 ± 0.20 | 1.4 ± 0.40 |
| Femur, fractured | 4.2 ± 1.04 | 4.0 ± 1.34 | 3.1 ± 0.70 | 2.5 ± 0.05 |
| Skeleton | 57.7 ± 5.54 | 46.6 ± 7.81 | 49.9 ± 5.44 | 38.0 ± 11.02 |
| Delayed retention index | 2.0 | 2.1 | 1.7 | 1.9 |

**[0040]** The composition pharmacokinetics study has shown that the composition distribution is characterized by the apparent osteotropicity. After the intravenous injection of the composition in the intact animals, in one hour, up to 48% of the injected activity localizes in the skeleton and 45% is excreted from the organism with the urine. In 3 hours after introduction the retention in the skeleton is 47%; the excretion is 30%. The activity level in blood quickly reduces; in 5 hours after the study start it is, practically, trace.

**[0041]** The composition supports the bone scintigraphy based on the bone pathology/norm delayed retention indexes. This confirms the functional eligibility of the composition as a radiopharmaceutical in diagnosing the osseous tissue pathologic processes accompanied with the osteoblastic processes.

## Claims

**1.** Metal complexes of the formula:

$$M(O)_K H_m A^{n-},$$

where M is an isotope of Tc, Re, Sm, Lu, Y,
H is the hydrogen, $A^{5-}$ is the anion of the zoledronic acid,
wherein, when M is the technetium, then K=1, m=1, n=2; when M is the rhenium, then K=1, m=1, n=1; when M is the samarium, lutetium, or yttrium, then K=0, m=1, n=1,
and their pharmaceutically acceptable salts, hydrates, or isomers.

**2.** Metal complexes in accordance with the claim 1, wherein the isotopes of metals are selected from the group consisting of the $^{186}Re$, $^{188}Re$, $^{99m}Tc$, $^{153}Sm$, $^{177}Lu$, $^{90}Y$.

**3.** Metal complexes in accordance with claim 1, wherein the isotopes of metals are selected from the group consisting of the $^{186}Re$, $^{188}Re$, $^{99m}Tc$.

**4.** Metal complexes in accordance with claim 3, wherein the reducing agent is the tin halogenide, sodium boron hydride, or sodium dithionite.

**5.** Metal complexes in accordance with the claim 3, wherein the selected tin halogenide is tin dichloride or tin fluoride.

**6.** Method of production of the metal complexes in accordance with claim 1, wherein the lyophilizate obtained by mixing the zoledronic acid and tin dichloride solution in the hydrochloric acid under inert gas and adding a hydroxide of an alkaline metal is mixed with a salt of a metal from the isotopes group and a radionuclide solution.

**7.** Radiopharmaceutical that contains the metal complexes, their pharmaceutically acceptable salts, hydrates, or isomers in accordance with claim 1, and an antioxidant.

**8.** Radiopharmaceutical in accordance with claim 7, wherein the antioxidant is selected from the group ascorbic acid or gentisinic acid.

**9.** Method of production of the radiopharmaceutical, wherein the lyophilizate is mixed with the solution containing the metal salt and the radionuclide solution.

**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/RU 2008/000748

A. CLASSIFICATION OF SUBJECT MATTER

C07F 5/00 (2006.01); C07F 13/00 (2006.01); A61K 51/00 (2006.01); A61P 35/04 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07F 5/00, 13/00, A61K 51/00, A61P 35/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PAJ, JOPAL, Esp@senet, C.A. (Chem.Abstr.), PatSearch, RUPAT, U.B.D.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | RU 2045282 C1 (INSTITUT BIOFIZIKI MZ RF) 10.10.1995, example 1 | 1-9 |
| Y | RU 2297229 C2 (NOVARTIS AG) 20.04.2007, the abstract, the description, p.5, line 50 | 1-9 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 10 June 2009 (10.06.2009) | 02 July 2009 (02.07.2009) |
| Name and mailing address of the ISA/ RU<br>Facsimile No. | Authorized officer<br>Telephone No. |

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## REFERENCES CITED IN THE DESCRIPTION

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